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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 263/32, 413/10, A61K 31/42 — A1

(11) International Publication Number: WO 98/55468

(43) International Publication Date: 10 December 1998 (10.12.98)

(21) International Application Number: PCT/JP98/02398

(22) International Filing Date: 1 June 1998 (01.06.98)

(30) Priority Data:
PO 7132 2 June 1997 (02.06.97) AU

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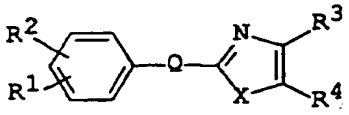
(81) Designated States: BR, CA, CN, JP, KR, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

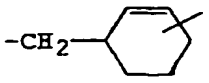
(54) Title: OXAZOLE COMPOUNDS USEFUL AS PGE2 AGONISTS AND ANTAGONISTS

(57) Abstract

Azole compounds of formula (I) wherein R^1 is lower alkyl substituted with carboxy, etc., R^2 is hydrogen or lower alkyl, R^3 is aryl, etc., R^4 is aryl, etc., Q is formula (a), etc., and X is O, NH or S, and its salts, which are useful as medicament.



(I)



(a)

DESCRIPTION

OXAZOLE COMPOUNDS USEFUL AS PGE2 AGONISTS AND ANTAGONISTS

TECHNICAL FIELD

This invention relates to azole compounds and its salts which are useful as a medicament.

BACKGROUND ART

Some azole compounds are known, for example, in WO 95/17393, WO 95/24393 and WO 97/03973.

DISCLOSURE OF INVENTION

This invention relates to azole compounds. More particularly, this invention relates to azole compounds and its salts which are useful as prostaglandin E_2 (hereinafter described as PGE_2) agonist or antagonists.

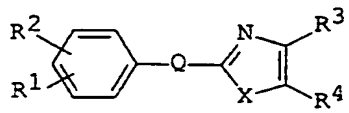
Accordingly, one object of this invention is to provide new and useful azole compounds and its salts.

Another object of this invention is to provide processes for production of the azole compounds or its salts.

A further object of this invention is to provide a pharmaceutical composition containing, as an active ingredient, said azole compounds or its salts.

Still further object of this invention is to provide use of the azole compounds and its salts for manufacture of medicaments for treating or preventing PGE_2 mediated diseases.

The azole compounds of this invention can be represented by the following formula (I) :



(I)

wherein R^1 is lower alkyl substituted with hydroxy, protected

PGE_2 is known as one of the metabolites in an arachidonate cascade. And it is also known that it has various activities such as pain inducing activity, inflammatory activity, uterine contractile activity, a promoting effect on digestive peristalsis, an awaking activity, a suppressive effect on gastric acid secretion, hypotensive activity, blood platelet inhibition activity, bone-resorbing activity, angiogenic activity, or the like.

PGE_2-sensitive receptors have been sub-divided into four subtypes, EP1, EP2, EP3 and EP4, and these receptors have a wide distribution in various tissues. The effects associated with EP1 and EP3 receptors may be considered as excitatory, and are believed to be mediated by stimulation of phosphatidylinositol turnover or inhibition of adenyl cyclase activity, with resulting decrease in intracellular levels of cyclic AMP. In contrast, the effects associated with EP2 and EP4 receptors may be considered as inhibitory, and are believed to be associated with a stimulation of adenyl cyclase and an increase in levels of intracellular cyclic AMP. Especially, EP4 receptor may be considered to be associated with smooth muscle relaxation, anti-inflammatory or pro-inflammatory activities, lymphocyte differentiation, antiallergic activities, mesangial cell relaxation or proliferation, gastric or enteric mucus secretion, or the like.

The azole compounds represented by the formula (I) or its salts possess binding activities to PGE_2-sensitive receptors, specifically to EP4 receptor, therefore they possess a PGE_2-antagonizing or PGE_2-inhibiting activity.

Therefore, the compounds represented by the formula (I) or its salts are useful for preventing or treating a PGE_2 mediated diseases, especially a EP4 receptors-mediated diseases, such as inflammatory conditions, various pains, or the like in human beings or animals.

More particularly, the compounds represented by formula

(I) and its salt are useful for treating or preventing inflammation and pain in joint and muscle (e.g., rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.), inflammatory skin condition (e.g., sunburn, burns, eczema, dermatitis, etc.), inflammatory eye condition (e.g., conjunctivitis, etc.), lung disorder in which inflammation is involved (e.g., asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.), condition of the gastrointestinal tract associated with inflammation (e.g., aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.), gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, allergic disease, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjögren's syndrome, Behcet disease, thyroiditis, type I diabetes, diabetic complication (diabetic microangiopathy, diabetic retinopathy, diabetic neohropathy, etc.), nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, kidney dysfunction (nephritis, nephritic syndrome, etc), liver dysfunction (hepatitis, cirrhosis, etc.), gastrointestinal dysfunction (diarrhea, inflammatory bowel diseases, etc.) shock, bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculosis, lithiasis (especially, urolithiasis), solid caricinoma, or the like in human being or animal.

In order to show the utility of the object compound (I), pharmacological data of the representative compounds thereof are shown in the following.

Binding assay using expression of prostanoide receptor subtype

[I] Test Compound :

(1) (S)-2-(4,5-Diphenyloxazol-2-yl)-1-(3-methoxybenzyl)-2-cyclopentene

(2) (S)-4-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}benzoic acid

(3) (S)-{3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}phenoxy}actamide

[II] Test Method :

The membrane fraction was prepared using COS-7 cells transfected prostanoide receptor sobtype (human EP4).

The Standard assay mixture contained membrane fraction, [^{3}H]-PGE_2 in final volume of 0.25 ml was incubated for 1 hour at 30°C. The reaction was terminated by that the mixture was rapidly filtered through a glass filter (GF/B). Then the filter was washed by 4 ml of ice-cold buffer at two times. The radioactivity associated with the filter was measured by liquid scintillation counting.

In the experiment for competition of specific [^{3}H]-PGE_2 was added at a concentration of 10 μM. The following buffer was used in all reactions.

Buffer: 20mM Mes (pH 6.0), 1mM EDTA, 10mM $MgCl_2$

The inhibition (%) of each compound at a concentration of 10μM was shown in Table.

[III] Test Result :

Test Compound	Inhibition(%)
(1) (10μM)	>80
(2) (10μM)	>80
(3) (10μM)	>80

Effect on IgE and IgG_1 secretion in mouse B lymphocytes

[I] Test Compound

Sodium (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoate

[II] Test Method

Inhibitory properties of a test compound against PGE_2-induced IgE and IgG_1 secretion in isolated resting B lymphocytes of mice were tested. Resting mouse B lymphocytes were isolated from spleens of 12-week-old BDF_1 male mice (Clea Japan Inc.) using adherent cell depletion, negative selection by FITC-anti-Thy 1.2 (30H12), FITC-anti-CD4 (GK1.5), FITC-anti-CD11b (M1/70) and FITC-anti-CD8a (5.-6.7) (Pharmingen) with anti-FITC Ab coating magnetic beads (PerSpective Daiagnostics) and Percoll gradient (Pharmacia). Resting B lymphocytes were cultured in flat-bottomed 96-well microtiter plates (Becton Dickinson) at 1×10^6 cells per ml and preincubated with a test compound or DMSO control for 30 minutes. Then PGE_2 were added at 10^{-6} M. After 1 hour, LPS and IL-4 were added and incubated at 37°C in a humidified atmosphere with 5% CO_2. After 6 days, supernatants were collected and IgE and IgG_1 were measured by the ELISA.

[III] Test Result

	$-PGE_2$	$+ 10^{-6}$ M PGE_2
IgE secretion (ng/ml)		
Control	27.6 ± 9.9	136.9 ± 22.2 #
$+ 10^{-5}$ M Test Compound	21.2 ± 5.7	37.0 ± 7.0 *
IgG_1 secretion (ng./ml)		
Control	680.1 ± 37.9	1970.7 ± 117.5 #
$+ 10^{-5}$ M Test Compound	1053.0 ± 176.2	1607.6 ± 150.9 #

Data : Mean ± S.E.M. (n = 4)

# $p<0.01$ v.s. Control ($-PGE_2$)

* $p<0.01$ v.s. Control ($+ 10^{-6}$ M PGE_2) (Dunett)

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form (e.g., tablet, pellet, troche, capsule, suppository, cream, ointment, aerosol, powder, solution, emulsion, suspension etc.), which contains the object compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient, suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation.

The pharmaceutical composition of this invention can contain various organic or inorganic carrier materials, which are conventionally used for pharmaceutical purpose, such as excipient (e.g., sucrose, starch, mannit, sorbit, lactose, glucose, cellulose, talc, calcium phosphate, calcium carbonate, etc.), binding agent (e.g., cellulose, methyl cellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose, starch, etc.), disintegrator (e.g., starch, carboxymethyl cellulose, calcium salt of carboxymethyl cellulose, hydroxypropylstarch,

sodium glycol-starch, sodium bicarbonate, calcium phosphate, calcium citrate, etc.), lubricant (e.g., magnesium stearate, talc, sodium laurylsulfate, etc.), flavoring agent (e.g., citric acid, mentol, glycine, orange powders, etc.), preservative (e.g., sodium benzoate, sodium bisulfite, methylparaben, propylparaben, etc.), stabilizer (e.g., citric acid, sodium citrate, acetic acid, etc.), suspending agent (e.g., methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agent, aqueous diluting agent (e.g., water), base wax (e.g., cacao butter, polyethyleneglycol, white petrolatum, etc.).

The effective ingredient may usually be administered with a unit dose of 0.01 mg/kg to 50 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight, conditions of the patient or the administering method.

The patents, patent applications and publications cited herein are incorporated by referance.

Abbreviations used in this application are as follows :

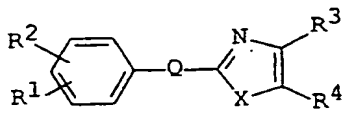
THF	:	Tetrahydrofuran
EtOAc	:	Ethyl acetate
Et_2O	:	Diethyl ether
DMF	:	N,N-Dimethylformamide
EtOH	:	Ethyl alcohol
MeOH	:	Methyl alcohol
AcOH	:	Acetic acid
nBuli	:	n-Butyllithium
MsCl	:	Methanesulfonyl chloride
pTsOH	:	p-Toluenesulfonic acid
$AcONH_4$	:	Ammonium acetate
DMAP	:	Dimethylaminopyridine
Pd/C	:	Palladium on carbone

$Pd(OH)_2/C$: Palladium hydroxide on carbone

The following Preparations and Examples are given only for the purpose of illustrating the present invention in more detail.

C L A I M S

1. A compound of the formula :



wherein

R^1 is lower alkyl substituted with hydroxy, protected carboxy or carboxy; carboxy; protected carboxy; carbamoyl; a heterocyclic group; cyano; halo(lower)alkylsulfonyloxy; lower alkoxy substituted with hydroxy or carbamoyl; aryl substituted with carboxy, protected carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with protected carboxy or lower alkylsulfonyl,

R^2 is hydrogen or lower alkyl,

R^3 is aryl optionally substituted with halogen,

R^4 is aryl optionally substituted with halogen,

Q is $-A^1-\overset{A^2}{\bigcirc}-A^3-$ [in which $-A^1-$ is a single bond or lower alkylene, $\overset{A^2}{\bigcirc}$ is cyclo(C_5-C_9)alkene, cyclo(C_3-C_9)alkane, bicyclo(C_6-C_9)alkene or bicyclo(C_5-C_9)alkane, and $-A^3-$ is a single bond or lower alkylene], and

X is O, NH or S,

and its salt.

2. A compound according to the claim 1, wherein

X is O.

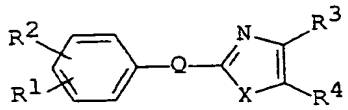
3. A compound according to the claim 2, wherein

R^1 is lower alkyl substituted with carboxy; carboxy;

protected carboxy; carbamoyl; a heterocyclic group; lower alkoxy substituted with carbamoyl; aryl substituted with carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with lower alkylsulfonyl.

4. A compound according to the claim 3, wherein
R^1 is lower alkyl substituted with carboxy; carboxy; carbamoyl; tetrazolyl; lower alkoxy substituted with carbamoyl; aryl substituted with carboxy or carbamoyl, and
Q is $-A^1-\overset{A^2}{\bigcirc}-A^3-$ [in which $-A^1-$ is methylene, $\overset{A^2}{\bigcirc}$ is cyclo(C_5-C_7)alkene, cyclo(C_5-C_7)alkane, bicyclo[2.2.1]heptene or bicyclo[2.2.1]heptane, and $-A^3-$ is a single bond].

5. A process for production of the compound of the formula :



(I)

wherein
R^1 is lower alkyl substituted with hydroxy, protected carboxy or carboxy; carboxy; protected carboxy; carbamoyl; a heterocyclic group; cyano; halo(lower)alkylsulfonyloxy; lower alkoxy substituted with hydroxy or carbamoyl; aryl substituted with carboxy, protected carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with protected carboxy or lower alkylsulfonyl,
R^2 is hydrogen or lower alkyl,
R^3 is aryl optionally substituted with halogen,

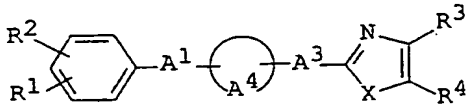
R^4 is aryl optionally substituted with halogen,

Q is $-A^1-\left(A^2\right)-A^3-$ [in which $-A^1-$ is a single bond or lower alkylene, $\left(A^2\right)$ is cyclo(C_5-C_9)alkene, cyclo(C_3-C_9)alkane, bicyclo(C_6-C_9)alkene or bicyclo(C_5-C_9)alkane, and $-A^3-$ is a single bond or lower alkylene], and

X is O, NH or S,

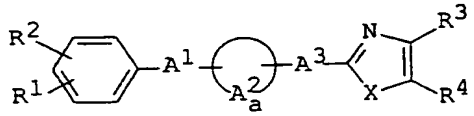
or its salt, which comprises,

(1) dehydrating a compound of the formula :



(II-1)

or its salt, to give a compound of the formula :



(I-1)

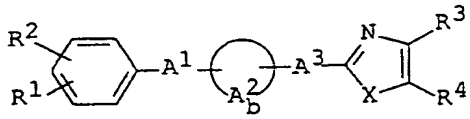
or its salt, in the above formulas,

R^1, R^2, R^3, R^4, $-A^1-$, $-A^3-$ and X are each as defined above,

$\left(A^2_a\right)$ is cyclo(C_5-C_9)alkene or bicyclo(C_6-C_9)alkene, and,

$\left(A^4\right)$ is cyclo(C_5-C_9)alkane or bicyclo(C_6-C_9)alkane, each of which is substituted with hydroxy,

(2) reducing the compound of the formula (I-1) defined above, or its salt, to give a compound of the formula :

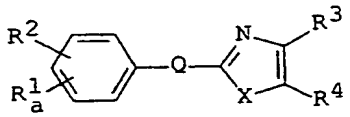


(I-2)

or its salt, in the above formula, R^1, R^2, R^3, R^4, $-A^1-$, $-A^3-$ and X are each as defined above, and

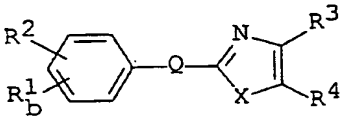
 is cyclo(C_5-C_9)alkane or bicyclo(C_6-C_9)alkane,

(3) subjecting a compound of the formula :



(I-3)

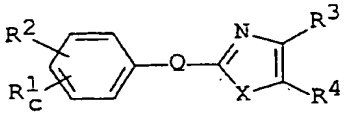
or its salt, to (a) a cleavage of ether bond and (b) a halo(lower)alkylsulfonylation, to give a compound of the formula :



(I-4)

or its salt, in the above formulas,
R^2, R^3, R^4, Q and X are each as defined above,
R^1_a is lower alkoxy, and
R^1_b is halo(lower)alkylsulfonyloxy,

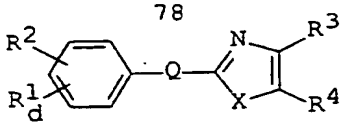
(4) subjecting the compound of the formula (I-4) defined above, or its salt, to Pd-catalyzed carbonylation, to give a compound of the formula :



(I-5)

or its salt, in the above formula,
R^2, R^3, R^4, Q and X are each as defined above, and
R^1_c is protected carboxy,

(5) subjecting the compound of the formula (I-5) defined above, or its salt, to deesterification, to give a compound of the formula :



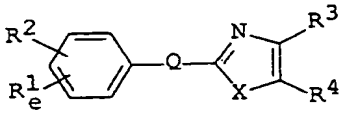
(I-6)

or its salt, in the above formula,
R^2, R^3, R^4, Q and X are each as defined above, and
R^1_d is carboxy,

(6) reacting the compound of the formula (I-6) defined above, or its reactive derivative at the carboxy group, or its salt, with a compound of the formula :

NH_3 (III)

or its reactive derivative, or its salt, to give a compound of the formula :

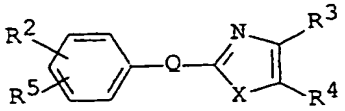


(I-7)

or its salt, in the above formulas,
R^2, R^3, R^4, Q and X are each as defined above, and
R^1_e is carbamoyl.

(7) reacting the compound of the formula (I-5) defined above, or its salt, with the compound of the formula (III) defined above, or its salt, to give the compound of the formula (I-7) or its salt, or,

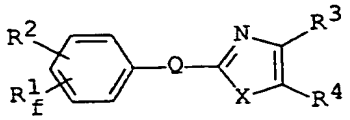
(8) reacting a compound of the formula :



(II-2)

or its reactive derivative at carboxy group, or its salt, with the compound of the formula (III)

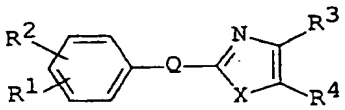
defined above, or its reactive derivative, or its salt, to give a compound of the formula :



(I-8)

or its salt, in the above formula,
R^2, R^3, R^4, Q and X are each as defined above,
R^1_f is lower alkoxy substituted with carbamoyl, and
R^5 is lower alkoxy substituted with carboxy or protected carboxy.

6. A Pharmaceutical composition containing a compound of the formula :



(I)

wherein
R^1 is lower alkyl substituted with hydroxy, protected carboxy or carboxy; carboxy; protected carboxy; carbamoyl; a heterocyclic group; cyano; hydroxy; halo(lower)alkylsulfonyloxy; lower alkoxy optionally substituted with hydroxy or carbamoyl; aryl substituted with carboxy, protected carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with protected carboxy or lower alkylsulfonyl,
R^2 is hydrogen or lower alkyl,
R^3 is aryl optionally substituted with halogen,
R^4 is aryl optionally substituted with halogen,
Q is $-A^1-\left(A^2\right)-A^3-$ [in which $-A^1-$ is a single bond or lower alkylene, $\left(A^2\right)$ is cyclo(C_5-C_9)alkene, cyclo(C_3-C_9)alkane, bicyclo(C_6-C_9)alkene or

bicyclo(C_5-C_9)alkane, and $-A^3-$ is a single bond or lower alkylene], and

X is O, NH or S,

or its salt, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

7. A use of the compound of claim 6 as a medicament.

8. A use of the compound of claim 6 as an agonist or an antagonist of PGE_2-sensitive receptor.

9. A method for treating or preventing PGE_2 mediated diseases which comprises administering an effective amount of a compound of claim 6 to human beings or animals.

10. The method for treating or preventing inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, allergic disease, cancer or neurodegenerative diseases which comprises administering an effective amount of a compound of claim 6 to human beings or animals.

11. A use of a compound of claim 6 for the manufacture of a medicament for treating or preventing PGE_2 mediated diseases in human beings or animals.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 98/02398

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/32 C07D413/10 A61K31/42

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 03973 A (FUJISAWA PHARMACEUTICAL CO ;TANIGUCHI KIYOSHI (JP); HATTORI KOUJI) 6 February 1997 cited in the application see claims 1-5,10-14; examples 32,34	1-11
X	WO 95 17393 A (FUJISAWA PHARMACEUTICAL CO ;TANIGUCHI KIYOSHI (JP); NAGANO MASANOB) 29 June 1995 cited in the application see the whole document	1-11
A	US 5 100 889 A (MISRA RAJ N ET AL) 31 March 1992 see the whole document	1-11

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 1998	31/08/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I. national application No.
PCT/JP 98/02398

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9 and 10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9 and 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

..formation on patent family members

Inter nal Application No
PCT/JP 98/02398

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703973 A	06-02-1997	AU 6469796 A	18-02-1997
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